Reconfiguration of functional brain networks underlying the distinctions between automatic and controlled handwriting

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Abstract

This study aimed to examine the brain mechanisms underlying the distinctions between automatic and controlled handwriting. Functional magnetic resonance imaging data were collected while adult participants (n = 53) performed a copying task with varying speed control demands. Network analysis showed significant differences in functional connectivity within and between the frontoparietal network (FPN), the default mode network (DMN), the dorsal attention network (DAN), the somatomotor network (SMN) and the visual network (VN) between automatic and speed-controlled handwriting irrespective of written materials, which are thought to reflect general executive control and task-relevant visuomotor operations. However, there were no differences in brain activation between automatic and controlled handwriting. These results suggest that reconfiguration of functional network architecture, rather than regional activation, underlies the dissociations between automatic and controlled handwriting. Our findings shed new light on the neural mechanisms of handwriting mastery and handwriting impairments in individuals with neurological disorders.

Introduction

Handwriting is a complex processing entailing cognitive, linguistic and perceptual-motor operations. Conceptually, handwriting is thought to be broadly divided into two distinct components: a central processing component for retrieving the correct orthographic form via orthographic long-term memory or phoneme-to-grapheme conversion; and a peripheral processing component for retrieval of written motor form via allographic/letter-shape conversion and for guiding of specific motor programs. At the neural level, handwriting requires the coordination of distributed neural systems, involving the frontal motor cortex, the intraparietal sulcus/superior parietal lobule, the inferior temporal gyrus (fusiform gyrus) and the cerebellum (Longcamp et al., 2014; Planton, Jucla, Roux, & Démonet, 2013; Planton, Longcamp, Péran, Démonet, & Jucla, 2017; Purcell, Turkeltaub, Eden, & Rapp, 2011; Rapp & Dufor, 2011; Vinci-Booher, Cheng, & James, 2018; Yang et al., 2018; Yang et al., 2019). Although multiple brain regions have been found to be involved in handwriting, the manners in which these brain regions interact with each other have rarely been examined.

For skilled writers, handwriting is highly automatic (Tucha, Mecklinger, Walitza, & Lange, 2006), and the automaticity of motor execution is an essential prerequisite to develop high level of handwriting skills, such as written composition (Connelly, Campbell, MacLean, & Barnes, 2006; Jones & Christensen, 1999; Stephen, 2006). At the same time, controlled processing is also engaged in some handwriting circumstances, such as attentively tracking writing speed (MacMahon & Charness,

2014). Undeveloped writers (Wicki & Hurschler Lichtsteiner, 2018) or individuals with neurological disorders (Broeder et al., 2014; Wu et al., 2016) are more likely to entail controlled processing during handwriting. From the perspective of motor control, automatic and controlled handwriting might refer the open-loop motor and closed-loop motor modes, respectively (Marquardt, Gentz, & Mai, 1999).

A few neuroimaging studies have examined the neural basis of the distinctions between automatic and controlled handwriting processes (Seitz et al., 1997; Hartwig R Siebner et al., 2001). In an emission tomography (PET) study, Siebner et al., (2001) found that controlled handwriting performance (write at half of normal speed) was associated with enhanced brain activation in the sensorimotor cortex, premotor cortex, supplementary motor area, anterior parietal cortex and the putamen. While, no particular regional activation was associated with automatic handwriting performance (write at normal speed). Brain activity in the bilateral inferior parietal cortex, the right premotor cortex and the left putamen increased during controlled handwriting, while the activation in the right primary sensorimotor cortex increased in automatic handwriting. Another PET study demonstrated the functional dissociation of the intraparietal sulcus between automatic and controlled handwriting processes: the anterior intraparietal sulcus is involved in controlled handwriting, while the posterior part of parietal cortex for automatic handwriting (Seitz et al., 1997). These findings suggest that multiple brain regions are preferentially engaged in either automatic or controlled handwriting processes.

From the network neuroscience perspective, the global reorganization of neural networks, rather than the regional activation, is adaptive to cognitive demands (Bressler & Menon, 2010; Olaf Sporns, 2014). Recent advances in the analysis of functional brain networks allow for characterizing the relationship between the dynamic interactions of brain networks and behaviors (Braun et al., 2015; Michael W. Cole et al., 2013; Finc et al., 2017; Spielberg, Miller, Heller, & Banich, 2015). For motor automaticity in particular, a prior study has demonstrated that visual-motor sequential learning is associated with functional segregation of visual and motor networks from the cognitive control networks, suggesting the shifts of functional networks related to the transition from controlled to automatic processing in visuomotor tasks (Bassett, Yang, Wymbs, & Grafton, 2015). Similarly, using a visuomotor association task, another study reported that motor practice strengthened the connectivity between the cingulo-opercular network (CON) and the dorsal attention network (DAN), but weakened the connectivity within the frontoparietal network (FPN) and its connectivity with the default mode network (DMN) (Mohr et al., 2016). These results suggest that the reconfiguration of functional networks might be associated with the dissociations between automatic and controlled handwriting.

Here, using fMRI, the present study sought to explore the manner in which the functional network reconfigures relates to the differences between automatic and controlled handwriting. The improvement of speed is a critical step for developing the

skill of automatic handwriting (Peverly, 2006). Following previous studies (Seitz et al., 1997; Hartwig R Siebner et al., 2001), we examined the differences between automatic and controlled handwriting circumstances via manipulating motor speed demands. Participants are required to perform a copying task at either natural or fast speed. In the fast speed condition, participants should pay extra attention to control motor speed, representing a controlled handwriting circumstance. While, writing at natural speed might resemble an automatic motor execution status (Hartwig R. Siebner et al., 2001). To examine whether the written material would influence the handwriting automaticity, both characters and non-sense symbols were included as written stimuli. In addition, word frequency was taken into account for the character material, as it has been found to interact with the motor execution during handwriting (Kandel & Perret, 2015; Qu, Zhang, & Damian, 2016; S. Roux, Mckeeff, Grosjacques, Afonso, & Kandel, 2013; Zhang & Cheng, 2014).

We expected to observe the differences in functional connectivity of the motor and visual networks between automatic and controlled handwriting, which are necessarily engaged in the handwriting processes (Planton et al., 2013; Purcell et al., 2011). Additionally, cognitive control networks (i.e. FPN) were also hypothesized to discriminate automatic and controlled handwriting, which have been found to be flexibly adopted for cognitive control demands (Bassett et al., 2015; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). Finally, to provide the activation context for the network analysis, the differences in regional brain activation between the natural

and fast handwriting conditions were also examined.

Methods

Participants

Fifty-three adults were recruited to participate in the study (27 males; mean age=22.3 years, range=19 to 28 years). All participants were native Chinese speakers and were right-handed as assessed by a handedness inventory (Snyder & Harris, 1993). The participants were physically healthy and reported no history of neurological disease or psychiatric disorder. The study was approved by the ethics committee of the Institute of Psychology, Chinese Academy of Sciences, and the methods were carried out in accordance with the approved guidelines. Free and informed consent was obtained from each participant prior to the experiment.

Stimuli and task procedure

Participants were instructed to perform a copying task. The stimuli were single Chinese characters and geometric symbols, including thirty characters and fifteen symbols. One half of characters were of "high frequency" and the other half were of "low frequency". High-frequency characters were chosen to occur ≥1500 times per million, and low-frequency characters to occur <5 times per million according to the *Modern Chinese Frequency Dictionary* (1986). The visual complexity of material was matched, which were indexed by the mean number of strokes. Participants were instructed to write characters or draw symbols with matched duration and size, while

minimizing movements of their upper arm and forearm (thus minimizing potential head motion artifacts in the fMRI data). Visual feedback was provided instantaneously in order to achieve a real handwriting situation. Moreover, brain blood oxygenation level-dependent (BOLD) single was more tightly correlated with behavioral performance with visual feedback relative to without visual feedback in fine motor tasks (Mayhew, Porcaro, Tecchio, & Bagshaw, 2017).

A block design was employed, consisting of six blocks of copying characters (three blocks for high- and low-frequency characters, respectively) and three blocks of drawing symbols, in a pseudo-random order. Each participant underwent two of these fMRI "runs", corresponding to two writing speed conditions: "natural" and "fast". For the natural condition, participants were instructed to write with the speed that they used in daily life. For the fast condition, they were instructed to write as fast as possible, but keep to write legibly. The order of the two writing speed conditions was counterbalanced across participants. The attributes of stimuli, including word frequency, visual complexity, were matched between the natural and fast conditions. Each block included visual presentation of instructions for 2 s followed by five trials. In each trial, a '+' symbol was first presented visually and centrally for 0.3 s, followed by presentation of a character stimulus for 0.8 s and then a response period of 4.5 s. Three blocks of central fixation each with 12 s duration were also interspersed among the task and control blocks as a "rest" condition in each run. The total duration of each run was 318 s.

Handwriting data were recorded using a tablet system specially developed for use in fMRI experiments. The tablet system includes a touch-sensitive surface, a force-sensitive stylus and an adjustable support frame, and is MRI-safe without significantly degrading fMRI data quality (Tam, Churchill, Strother, & Graham, 2011). The support frame was adjusted carefully for each participant to ensure that handwriting and drawing could be undertaken comfortably throughout the imaging session, and to enable tablet interaction with the forearm or wrist resting on the support such that there was no fatigue from handwriting against gravity.

Imaging acquisition

Imaging was performed at 3T using an MRI system (MAGNETOM Prisma[fit], Siemens, Erlangen, Germany) at the Beijing MRI Center for Brain Research of the Chinese Academy of Sciences. Functional MRI time series data with BOLD contrast were acquired using a two-dimensional, T2*-weighted, gradient-echo echo planar imaging (EPI) sequence (Moeller et al., 2010) (repetition time TR = 1000 ms, echo time TE = 30 ms, slices thickness = 2.2 mm, in-plane resolution=2.2 mm x 2.2 mm, flip angle θ = 45°). Sixty-four axial slices were collected. High spatial resolution anatomical images were acquired using a three-dimensional T1-weighted, magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 2200 ms, TE = 2.08 ms, slice thickness = 1 mm, in-plane resolution = 1.0 mm x 1.0 mm and θ = 8°).

Post-imaging behavioral tests

First, to link the neural activity with the normal handwriting performances, pen-and-paper writing tests were administered to all participants that required them to copy 80 Chinese characters using 'natural' and 'fast' writing style, respectively. Half of the characters were high-frequency characters, and half were low-frequency characters. The order of the two writing conditions was counterbalanced across participants.

Second, a batch of behavioral tests was employed to examine the skills related to handwriting (Yang et al., 2020). First, visual orthographic recognition was evaluated by using a radical search task, in which participants were required to mark characters with a specific radical ('木', mu4, wood) from 180 randomly arranged characters that might or might not include the designated radical (Siok & Fletcher, 2001). One correct mark scored 1 point. In addition, sustained attention capacity was assessed by using a cancellation test, in which participants were instructed to search and mark the target number ('3') as quickly and accurately as possible within 3 minutes. The score was calculated by this equation: score = attack -(false alarms+0.5*omission). Finally, low-level visual-motor skill was employed using a visual-motor integration test in which participants were asked to copy 12 geometric symbols varying in visual complexity as accurately as possible. Two independent evaluators assessed the similarity between samples and participants' responses using a 7-point scale, and the score was the sum of each symbol.

Data analysis

Behavior data. For the behavioral data, we collected data on writing duration and writing latency. The writing duration was defined by the interval from the start of the response period (first contact with the tablet) to the end of the last stroke of the response, while the writing latency was defined by the time period between the onset of the response screen and the first contact with the tablet. We first examined the differences in writing duration between the natural and fast conditions for each participant, ensuring that participants consistently increased their writing speed in the fast condition as opposed to the natural condition. Then, a 3 (stimulus type: high-frequency character, low-frequency character and symbols) by 2 (writing speed: natural and fast) analysis of variance (ANOVA) was conducted for writing latency and duration, respectively.

In addition, the mean completion time and standard deviations (SD) of the post-imaging pen-and-paper writing test, as well as the scores of behavioral tests were calculated.

Image data.

Preprocessing. Image preprocessing and statistical analyses were conducted using SPM8 freeware (http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Department of Cognitive Neurology, University College London, London). The fMRI time series data for each participant were first corrected for head motion, and the corrected images were co-registered to the associated anatomical imaging data. The anatomical images were transformed into Montreal Neurological Institute (MNI) stereotactic space, and the resulting transformation parameters were then applied to yield fMRI time series data

normalized in MNI space with cubic voxels at 2 mm × 2 mm × 2 mm spatial resolution. These images were then spatially smoothed using an isotropic Gaussian kernel template with 6 mm full-width at half-maximum. The data for one participant were not examined further because the exclusion criteria for head motion were exceeded (>3 mm translation or > 3º rotation). Data for another participant were excluded due to substantial signal loss in the prefrontal cortex.

Network construction. The nodes were defined as 10-mm diameter spheres, based on a functional brain parcellation which consists of 264 regions of interests (ROIs) (Power, Cohen, Nelson, Wig, & Petersen, 2011). The estimated functional connectivity (FC) matrices for each task condition was created using CONN Functional Connectivity Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). Specifically, the BOLD time series were first divided into six task conditions according to the onset and duration of each condition. The effect of nuisance covariates, including fluctuations in BOLD from cerebrospinal fluid, white matter and their derivatives, were estimated and removed using the anatomical component correction (CompCor) strategy (Behzadi, Restom, Liau, & Liu, 2007). The head motion noises (estimated with six degrees of freedom during the motion correction step) were also included as nuisance. The task effects of each condition convolved with a hemodynamic response function and their first-derivative terms were also regressed out, and this procedure has been evidenced in resulting a high level of reliability of graph theoretical analysis (H. Cao et al., 2014). The resulting residual time series were high-pass filtered at 0.008 Hz for preserving the

task-relevant high-frequency signals (Finc et al., 2017; Xin Liu et al., 2018). Pearson's correlation coefficients between each pair of nodes were computed, which were transformed into Fisher's z scores, resulting in undirected and weighted 264×264 FC matrices for each participant and each condition (Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015a). The significant nonzero connections in FC matrices for each condition were computed by performing one-sample t-tests ($p < 0.05$, uncorrected) using the GRETNA toolbox (http://www.nitrc.org/projects/gretna/) (Wang et al., 2015).

Network-based statistics. The network-based statistical analysis (NBS) was applied to identify the specific functional networks that discriminate automatic and controlled handwriting. NBS is a statistically powerful approach for identifying the specific connections within brain networks for the differences between psychological contexts (Andrew Zalesky, Fornito, & Bullmore, 2010). The analysis was constrained within a mask including significant nonzero connections across the participants and conditions, ensuring that statistical comparisons were based on the same network space (Jiang et al., 2013; Wagner et al., 2019). A repeated-measures ANCOVA with stimulus type and writing speed as within-subject factors was conducted. To account for the differences in behavioral performances during fMRI scan, handwriting latency and motor duration were included as covariates. Additionally, because robust sex difference has been repeatedly reported in handwriting (Reilly, Neumann, & Andrews, 2019; Reynolds, Scheiber, Hajovsky, Schwartz, & Kaufman, 2015; Yang et al., 2020), sex was also

incorporated as a covariate. A set of supra-threshold connections were defined ($p <$ 0.01), which were used to determine the topological components and their intensity-based sizes (the sum of test statistic values across all connections within a component) (Q. Cao et al., 2013; Spies et al., 2019; A. Zalesky, Cocchi, Fornito, Murray, & Bullmore, 2012). Then, nonparametric permutation tests were performed to estimate the significance of each component (permutation times=5000, FWER-corrected $p <$ 0.05). For each permutation, conditions were randomized under the null hypothesis without affecting the test statistic (A. Zalesky et al., 2012). Finally, the corrected p value for a component of given size was calculated as the proportion of permutations for which the largest component was the same size or greater.

In addition, the hubs were defined as those nodes whose strength were 1.5 SD greater than the mean strength across all nodes in the network (X. Liu et al., 2018; O. Sporns, Honey, & Kotter, 2007). The node strength is analogous to node degree in weighted networks and is defined as the sum of edge weights attached to a node (Fornito, Zalesky, & Bullmore, 2016).

Validation analysis. To ensure that the results were not biased by the use of a single threshold, the above analyses were validated using different thresholds (Liang, Zou, He, & Yang, 2016). Specifically, we applied both the raw FC matrices and significant FC matrices thresholded at p<0.05 FDR corrected, to the NBS analysis, respectively.

Correlations between functional connection strength and behavior

Correlation analysis was conducted between the mean connection strength and the changes of handwriting speed during pen-and-paper. The mean connection strength was defined as the average of weights of all edges in the networks, and the changes of writing speed was defined by this equation: (natural handwriting duration - fast handwriting duration)/natural handwriting duration.

In addition, the correlation between the connection strength and the performances of sustained attention, visual orthographic recognition and visual-motor skill was also examined. The statistical significance was set at $p < 0.05$, uncorrected for the multiple comparisons.

Regional activation analysis. To illustrate the activation patterns of handwriting and the possible differences in brain activation between the two handwriting conditions, whole-brain brain activation analysis was employed. At the individual level, activation maps contrasting copying characters and drawing symbols to 'rest' were generated for each participant using the general linear model (GLM) method. The GLM design matrix included the block design time series convolved with a canonical hemodynamic response function. To minimize residual motion artifacts, head movement parameters (estimated with six degrees of freedom during the motion correction step) were included in the design matrix as nuisance covariates. The data were high-pass filtered at 0.008 Hz. Group analyses of the brain activation for each condition were performed

using a one-sample t-test, and then the activation maps were entered into a random-effects ANCOVA to examine the effects of stimulus type (high-frequency character vs. low-frequency character vs. symbol) and writing speed (natural vs. fast), with sex and in-scanner behavioral performances (latency + duration) as covariates. The voxel-wise threshold for statistically significant activation was set at $p < 0.05$, corrected for multiple comparisons using the family-wise error (FWE) with a minimum cluster extent of 20 contiguous voxels. Brain regions were estimated from the Talairach atlas (Talairach & Tournoux, 1988).

Results

Behavioral results

In-scanner behavioral performances. Four participants did not exhibit increases in handwriting speed (fast > natural), suggesting that they might not follow the task instruction or they adopted different handwriting strategies. To keep the consistency of responses across participants, their data were excluded for the following analysis. In addition, two participants were excluded after screening for fMRI data quality issues as described in the Preprocessing section above. The reported behavioral and fMRI results were based on the remaining 47 participants.

Writing duration and latency for each condition were presented in Figure 1A. For the writing duration, we found significant main effects of stimulus type [$F(2, 92)=27.27$, $p<0.001$] and writing speed [$F(1, 46)=152.83$, $p<0.001$]. Post-hoc pairwise

comparisons of stimulus type showed that the duration of drawing symbol was significantly longer than handwriting high-frequency character ($p < 0.001$) and low-frequency characters ($p < 0.001$), and the duration of handwriting low-frequency character was longer than handwriting high-frequency characters ($p < 0.001$). Post-hoc pairwise comparisons of speed condition indicated that the duration of fast handwriting was significantly shorter than the natural handwriting ($p < 0.001$). The mean (SD) changes in duration was 28 % (13.29%) in the high-frequency character condition, 27.38 % (14.45%) in the low-frequency character condition and 27.54% (16.17%) in the symbol condition. However, the interaction between the stimulus type and writing speed was not significant [$F(2, 92)=1.79$, $p =0.173$].

For the writing latency, neither the main effect of stimulus type [$F(2, 92)=0.03$, $p=0.972$], the main effect of writing speed [$F(1, 46)=0.11$, $p=0.743$] nor their interaction was significant [$F(2, 92)=1.93$, $p=0.151$].

Out-scanner behavioral performances. In the natural handwriting condition, the mean completion time (SD) of high-frequency and low-frequency characters was 51.49 s (8.77 s) and 50.78 s (9.66 s), respectively. In the fast writing condition, the mean completion time of high-frequency and low-frequency characters was 34.68 s (6.48 s) and 39.78 s (8.09 s) (Figure 1B). The mean (SD) speed changes during pen-and-paper handwriting was 32.21 % (9.05%) for the high-frequency characters, and was 20.69 % (13.32 %) for the low-frequency characters. The mean score (SD) of sustained attention

was 44.69 (3.32). The mean score (SD) of visual orthographic recognition was 80.98 (10.77) and the mean score (SD) of visual-motor integration was 48.41 (7.74). The inter-rater reliability of the assessment of visual-motor integration was good (intra-class correlation coefficients (ICC) = 0.86).

Functional network analysis results

To refer the results of networks to well-known functional systems, they were assigned to the networks divisions defined previously (M. W. Cole et al., 2013; J. D. Power et al., 2011). A large-scale functional network was engaged in handwriting character and symbols, mainly involving the FPN, DMN, CON, visual network (VN) and somatomotor network (SMN). ANCOVA analysis indicated that no functional networks were detected for the interaction between stimuli type and handwriting speed. A network (183 nodes and 229 edges) was identified for the main effect of handwriting speed, involving intranetwork connectivity within the FPN and DMN, and internetwork connectivity between the FPN and DMN, between the FPN and VN, between the DMN and SMN, and between the VN and SMN (Figure 2A). Additionally, a significant main effect of stimulus type was characterized by a network of clustering 226 nodes and 446 edges, mainly involving intranetwork connectivity within the FPN and DMN, as well as internetwork connectivity between the FPN and DMN, between the SMN and DMN, and between the SMN and DAN (Figure 2B). The results were visualized by using BrainNet Viewer (Xia, Wang, & He, 2013).

Post-hoc comparisons further identified the networks preferentially related to automatic and controlled handwriting processes, respectively. The "fast > natural" contrast revealed a network (90 nodes and 81 edges) resulting from the speed control demand, involving the intranetwork connectivity within the DMN, as well as the internetwork connectivity between the DMN and FPN, between the DMN and the right SMN, between the left SMN and right VN, between the left SMN and right DAN, and between the left VN and right DAN. Several brain regions were identified as hubs, including the bilateral precuneus and cingulate gyrus (CG), the left superior frontal gyrus (SFG), middle frontal gyrus (MFG) and the right superior parietal lobule (SPL) (Figure 3A). The contrast "natural > fast", on the other hand, revealed a network preferentially related to automatic handwriting (107 nodes and 122 edges), mainly encompassing the intranetwork connectivity within the FPN, and internetwork connectivity between the FPN and VN, between the FPN and DAN and between the left SMN and the left DMN. Several regions were identified as hubs, including the bilateral MFG and precentral gyrus (PreCG), the left fusiform gyrus (FG), precuneus and inferior occipital gyrus (IOG) and the right inferior parietal gyrus (IPL), middle occipital gyrus (MOG), cuneus and CG (Figure 3B).

Validation analysis indicated that these results largely overlapped when different thresholds were used for defining the edges (Appendices Figure A1).

Correlations between functional connectivity strength and behavior

Correlation analysis revealed that the decrease in duration during pen-and-paper handwriting was negatively correlated with the connectivity strength of the networks for controlled handwriting (fast > natural) ($r = - 0.32$, $p = 0.029$), and the connectivity strength of the networks for automatic handwriting (natural > fast) contrast ($r = - 0.48$, $p < 0.001$) (Figure 4A).

In addition, the connectivity strength of networks for controlled handwriting was negatively correlated with the attention score (r = -0.32, $p = 0.029$), but the correlation was not observed in the network for automatic handwriting (r = -0.04, $p = 0.767$) (Figure 4B). No significant correlations between functional connectivity and visual orthographic recognition and visual-motor integration were found.

Brain activation analysis

One-sample *t* tests showed a similar activation pattern for handwriting and drawing symbols, involving the bilateral SFG, MFG, inferior frontal gyrus (IFG), PreCG, middle/inferior temporal gyrus (MTG/ITG), SPL/IPL, postcentral gyrus (PostCG), precuneus, MOG/IOG, FG, lingual gyrus (LG), cuneus, cerebellum and thalamus (Figure 5A). Significant main effect of stimulus type was observed in activation in the bilateral SFG/MFG/IFG, PreCG, superior temporal gyrus (STG), MTG/ITG, SPL/IPL, PostCG, precuneus, MOG/IOG, FG, LG, cuneus and cerebellum (Figure 5B). However, no brain activation was identified for the main effect of writing speed or the interaction between stimulus type and writing speed.

Discussion

The aim of study is to identify the reconfiguration of functional networks that differentiates automatic and controlled handwriting. We found that the functional connectivity within and between the FPN, DMN, DAN, SMN and VN preferentially involved in either automatic or controlled handwriting, irrespective of the written material. The result suggests that automatic and controlled handwriting differ in both the general executive control and task-specific visual and motor processes. Moreover, the shifts of functional networks were related to the performances of pen-and-paper handwriting, confirming the significances of the dynamic reorganization of functional networks in real-life handwriting behavior. Unexpectedly, we found that the shifts of functional networks between automatic and controlled handwriting were not modulated by the written material. This result suggests that motor speed control might be an independent factor of handwriting motor. Taken together, the present study for the first time reveals the differences in functional networks between automatic and controlled handwriting, advancing our understanding of the neural basis of handwriting expertise.

For the behavioral results, we analyzed writing latency and motor duration during fMRI scan. The former is informative for the central processing, and the latter for the peripheral motor processing (Kandel & Perret, 2015). Significant differences were detected in writing duration but not in the writing latency between the natural and fast conditions, suggesting that the observed differences in functional networks are likely

attributed to motor execution processing, rather than visual word recognition.

The controlled-oriented functional networks

First, we found that the connectivity within the DMN was enhanced in the fast condition relative to the natural condition, centering on the precuneus and CG. The controlled processing in the fast condition was supported by the significant correlation between the functional connectivity strength and the sustained attention score. The increased connectivity within the DMN in speed-controlled condition coincides with the evidence from brain activation studies reporting increased activation in the precuneus during controlled handwriting (Hartwig R Siebner et al., 2001). Although DMN has traditionally found to be a task-negative functional network (Fox, Snyder, Vincent, & Maurizio, 2005; Raichle et al., 2001), there is ample evidence showing that DMN is functionally involved in a wide range of cognitive tasks (Crittenden, Mitchell, & Duncan, 2015; Spreng et al., 2010; Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015b). Particularly, DMN has been found to be positively active in internally focused processes (Beal et al., 2011; Kam et al., 2019). Thus, it is logical to observe the increased intranetwork connectivity within the DMN in the speed-controlled condition. In the present study, participants were required to attentively track the motor speed without external cues. They had to attentionally monitor their speed by referring to their own feeling, which might trigger significant self-reference processing or internal attention.

In addition, we found that the connectivity between the DMN and FPN increased in the fast condition relative to the natural condition. The left MFG, SFG and SPL have been identified as hubs. This result corresponds to the findings showing the enhanced connectivity between the FPN and DMN with the increase of working memory load (Finc et al., 2017; Liang et al., 2016; Zuo et al., 2019).The FPN has been found to dynamically interact with other networks adapted to different task demands (Michael W. Cole et al., 2013; Dosenbach et al., 2007; Spreng et al., 2010). The coupling between the FPN and DMN is thought to support the introspective processes (Dixon et al., 2018). Thus, the enhanced connectivity between the FPN and DMN might also be recruited to meet the increased demand of internal attention processing under the controlled context.

Finally, we found the internetwork connectivity between the SMN and VN enhanced in the fast condition, which might represent task-relevant functional integration for speed control during handwriting. Previous brain activation studies have demonstrated that the activity in somatosensory and motor regions were positively correlated with the increase of movement rate in simple hand tapping tasks (Sadato et al., 1997; Seidler, Noll, & Thiers, 2004; Turner, Grafton, Votaw, Delong, & Hoffman, 1998). Meanwhile, the visual regions, particularly the left LG, are essential for orthographic recall during handwriting (Rapp & Dufor, 2011; Rapp & Lipka, 2011). Moreover, the activity visual regions were found to increase with the increasing of attentional demand in a visual search task (Mayer et al., 2007). Accordingly, the increased connectivity between SMN and VN suggests that task-relevant motor and visual networks should become

integrative when speed control is demanding. This interpretation is in accordance with previous findings demonstrating that the functional integration between motor and visual networks decreased as finger motor sequence became more automatic (Bassett et al., 2015). Alternatively, the alternations of connectivity between VN and SMN might be associated with the requirement of feedback processes under the controlled handwriting. Visual feedback plays an pivotal role in handwriting that mediates writing performance by providing an online inspector to modify writing gestures and speed (Danna & Velay, 2015). Fast handwriting condition presumably approximates a closed-loop motor model, while the natural (automatic) handwriting represents an open-loop motor model. Feedback control is particularly important for the closed-loop motor control (Marquardt et al., 1999). Accordingly, the strengthened functional integration between the SMN and VN might reflect the high demand for integration between somatosensory and visual feedbacks. Moreover, the connectivity of the DAN with the SMN and VN increased in the controlled handwriting condition. DAN is actively related to the goal-oriented attentional control (Shulman & Corbetta, 2002). With the increase of speed control demand, the DAN might be much recruited to inspect the outputs of motor and visual processing.

The automatic-oriented functional networks

First, we found the connectivity within the FPN increased during automatic handwriting, centering on the PreCG, MFG and IPL. MFG and the PreCG have been repeatedly reported to be engaged in handwriting (Planton et al., 2013; F. E. Roux et al., 2009). In

addition, previous studies have demonstrated the functional distinctions between the superior and inferior parietal cortex in closed-loop vs. open-loop motor control. Specifically, the IPL is more important for open-loop control processing (Macuga & Frey, 2014). Thus, our findings are in line with this functional division of parietal cortex showing that the connectivity of the IPL was more essential for automatic handwriting, while the SPL was for controlled handwriting. Functionally, the FPN has been found to support the chunk segmentation (parsing contiguous motor into shorter action sets) during hand motor processing, which represents the formation of ordered action boundaries (Wymbs, Bassett, Mucha, Porter, & Grafton, 2012). It has been proposed that during slow motor processing, the motor patterns and consequently the segmented processing might be more involved relative to fast motor processing (Schenk, Walther, & Mai, 2000). Thus, the enhanced connectivity within the FPN during automatic handwriting might attributed to the high level of motor chunk segmentation processing.

In addition, we found that the connectivity of the FPN with DAN was relatively strong during automatic handwriting. FPN has been suggested to be involved in global visual-spatial attention for motor monitor (Ptak, Schnider, & Fellrath, 2017; Schnell et al., 2007). Thus, the relatively increased functional integration between the FPN and DAN probably reflects the functional integration of attention during automatic handwriting. We speculated that automatic handwriting might need more global attentional monitor for the written outputs, because multiple dimensions of handwriting processing including size, speed and pressure are needed to inspected. While in the fast

handwriting condition, only a specific factor of motor speed was required to be attentively tracked. The increased connectivity between FPN and VN during automatic handwriting suggests that participants may pay more attention to inspection of visual outputs under natural condition compared to controlled handwriting condition. This notion is in line with previous findings indicating that FPN supports the sustained action monitoring and detection of incongruence between the subjects' own actions and visually perceived actions during visual-motor processing (Schnell et al., 2007).

Brain activation analysis

The whole-brain activation analysis identified a distributed and similar neural circuits for characters and symbols, consistent with the findings of previous studies (Harrington, Farias, Davis, & Buonocore, 2007; Yuan & Brown, 2015). Surprisingly, we did not observe the difference in brain activation between normal and fast conditions. This result is in contrast to previous findings reporting that the activation in the left premotor cortex and the left frontomesial cortex was greater in the fast or slow (controlled) handwriting condition than the natural (automatic) handwriting condition (Seitz et al., 1997; Hartwig R Siebner et al., 2001). The discrepancy might be due to the task design between these studies. Firstly, the task difficulty is different. A very simple writing task (writing single letter) was used in Seitz et al., (1997) and Siebner et al., (2001) studies, but a continuous and complex writing task (Chinese characters and symbols) was adopted in the present study. A strong and distributed brain activation was found in each condition in this study, which might shade the difference in brain activation between

speed conditions. In addition, the decrease of mean writing duration from the exact condition to the fast condition was more than 60 % in Siebner et al., (2001), whereas a decrease rate of only 28 % and 27 % was observed for high-frequency and low-frequency characters in the present study, respectively. Thus, the differences in operation efforts between the natural and fast writing conditions in the present study may not be sufficient for tapping the differences in brain activation. This notion is consistent with previous studies of motor processing, showing that finger movement with the dominant hand produced relatively weak activation changes in the cerebellum for different motor frequencies (Jäncke, Hänggi, & Steinmetz, 2004). Further studies with designing more speed levels are needed to address this question.

Methodological implications

Our results have methodological implication for the neuroimaging studies of handwriting. Self-paced (natural) handwriting (Berninger, Richards, & Abbott, 2015; Longcamp et al., 2014; Planton et al., 2017) and fast-paced handwriting (Dufor & Rapp, 2013; Karimpoor et al., 2018; Palmis et al., 2019) are two commonly used task paradigms in neuroimaging studies of handwriting. Our findings suggest the two handwriting status might recruit different functional networks, which could be used to explain the differences in results of previous findings. In addition, handwriting tasks have been widely used as clinical tests in individuals with neurological disorders (Fuentes, Mostofsky, & Bastian, 2009; Mergl et al., 2004; Morrens, Hulstijn, & Sabbe, 2006; Nackaerts et al., 2013). Our findings highlight the importance of considering the

differences in handwriting paradigms (self-paced vs. fast-paced) for examining specific

functional networks impaired in various neurological disorders.

Conclusion

Using functional network analysis, this study characterizes the transitions of functional

network architecture underlying the dissociations between automatic and controlled

handwriting. Our findings indicate that handwriting speed control relies on a large-scale

reorganizations of functional network, including the FPN, DMN, DAN, SMN and VN.

These findings advance our understanding of the neural basis of handwriting expertise

and the causes of handwriting difficulty in individual with neurological disorders.

Acknowledgements

Conflict of Interest Statement

The authors declare no conflict of interest

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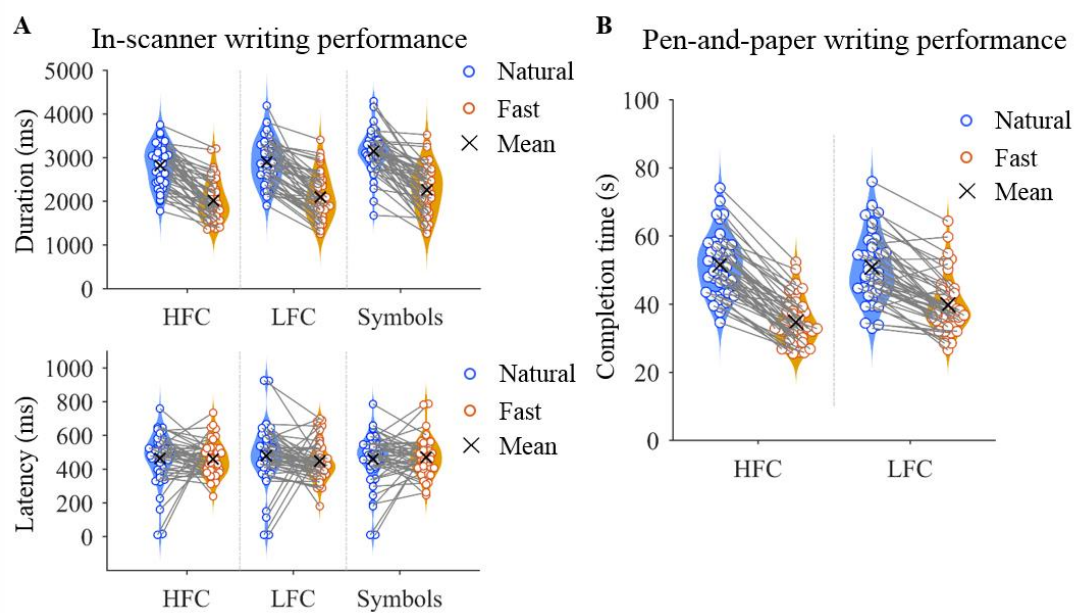
Figure 1 Behavioral results. (A) Writing duration and latency during fMRI. (B) The completion time of pen-and-paper writing. HFC = high-frequency characters, LFC = low-frequency characters, ms = millisecond.
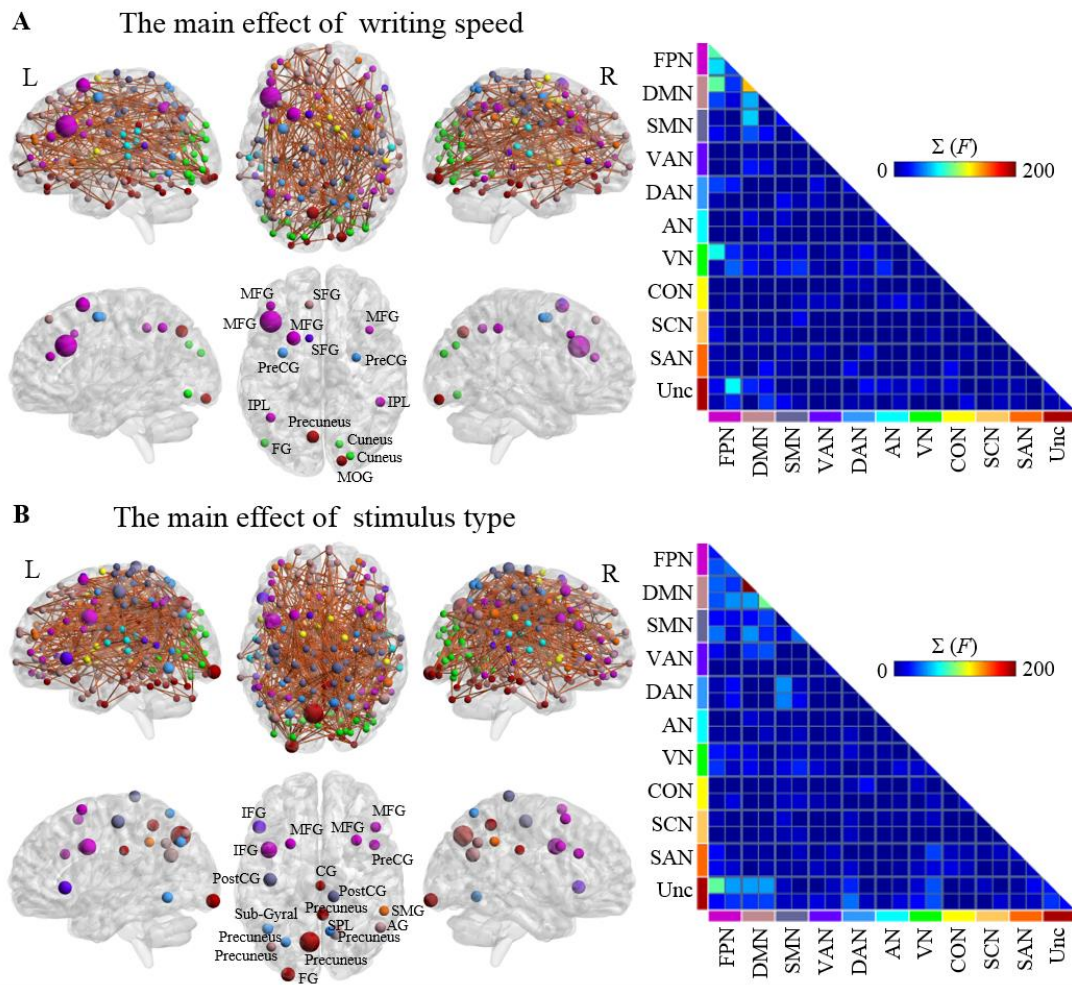
Figure 2 Networks for the main effect of writing speed (A) and stimuli types (B). The colors of the nodes in the brain plots indicate the network (coded by color bands along the matrix edges) to which they belong. Hubs in the networks were shown in the bottom panel, whose sizes are proportional to the node strengths. The matrix plots in the right panel represent connectivity strength between pairs of the 11 brain networks. Within each network, left hemispherical nodes are at the top (left) while right hemispherical nodes are at the bottom (right), separated by thin lines. The color of each element in the matrices represent the sum of the weight of all the edges for the connected networks. L = left and R = right, HFC = high-frequency characters, LFC = low-frequency characters. FPN = frontal-parietal network, DMN = default network, SMN = somatosensory

network, VAN = ventral attention network, DAN = dorsal attention network, AN = auditory network, VN = visual network, CON = cingulo-opercular network, SCN = subcortical network, SAN = salience network and Unc = Uncertain.
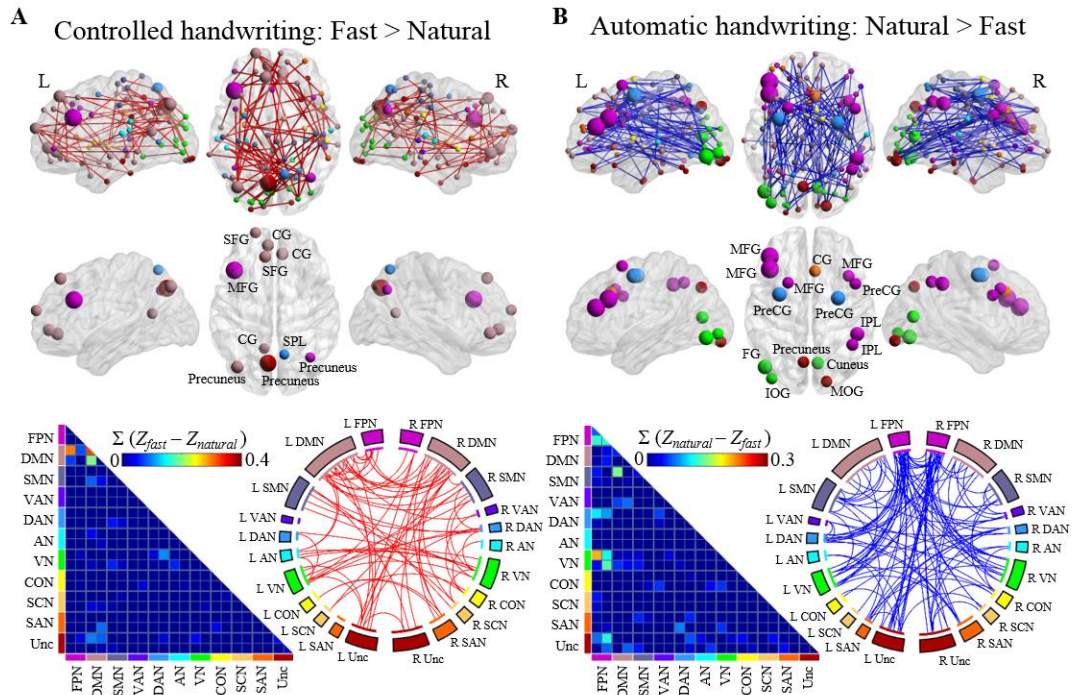
Figure 3 The differences in functional networks between automatic and controlled handwriting processes. The functional networks preferentially related to controlled handwriting (A) and automatic handwriting (B). The network hubs were shown in the middle panel and the node importance is represented by node size. The matrix plots in the bottom panel represent connectivity strength between pairs of 11 brain networks. The color of each element denotes the sum of the weight of all the edges. The circle plots represent the connectivity patterns.
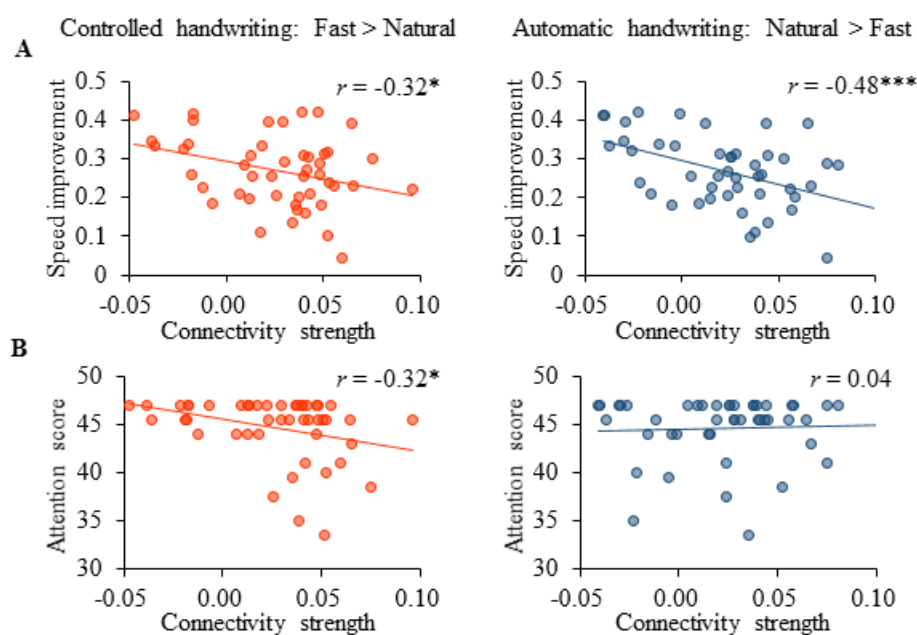
Figure 4 The correlations between the connectivity strength (networks for controlled handwriting / networks for automatic handwriting) and the changes of writing speed during pen-and-paper handwriting (A) and the attention score (B). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
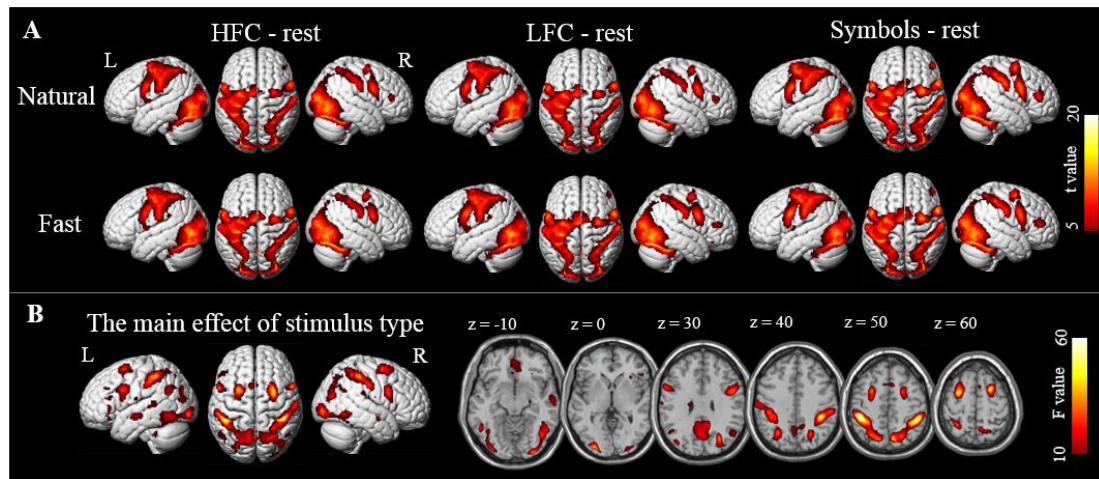
Figure 5 The results of voxel-wise multivariate analysis. Rendered view of the brain regions with significant activation for handwriting and drawing symbols in the natural and fast conditions (A) and the brain regions with a significant main effect of stimulus type (B). Statistical maps were thresholded at voxel-wise $p < 0.05$, FWE-corrected with a minimum cluster extent of 20 contiguous voxels. In the legend, '+' indicates positive correlation between the brain activation and the copying speed under the corresponding condition, while '-' indicates negative correlation. L = left and R = right. HFC = high-frequency characters, LFC = low-frequency characters. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.
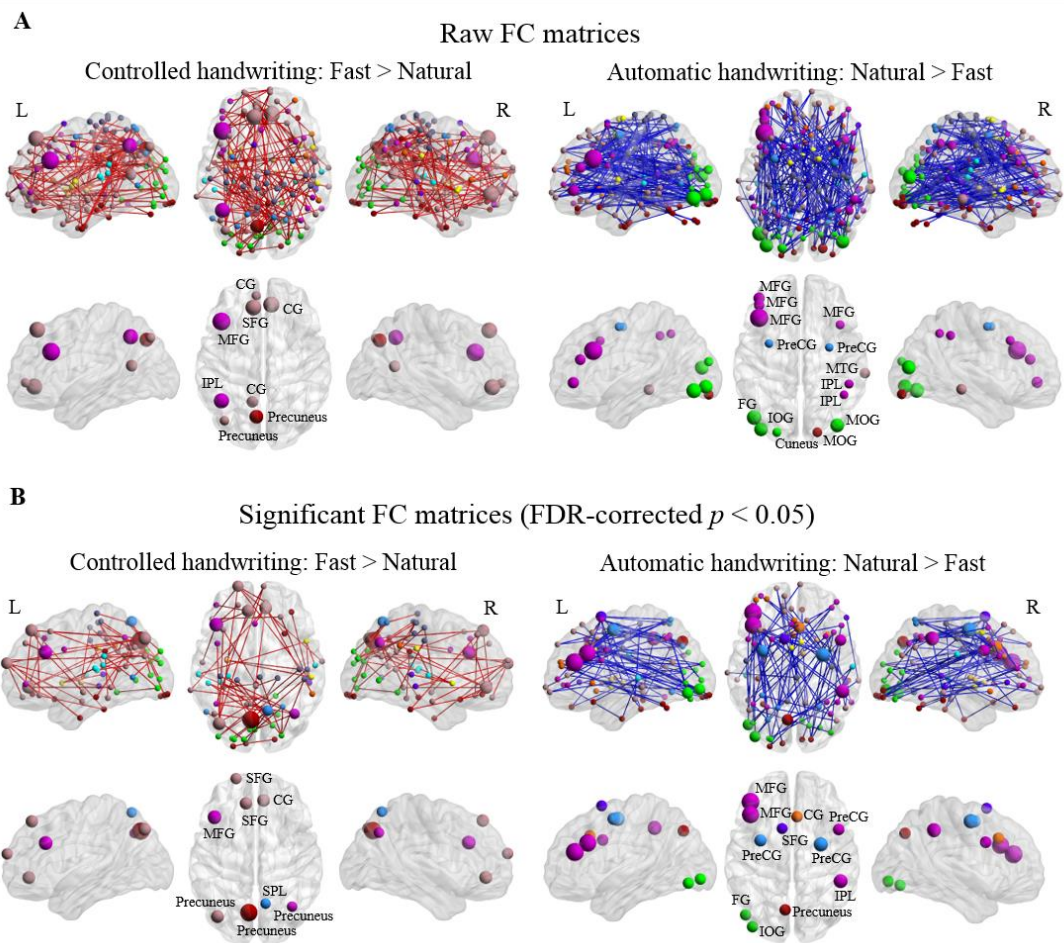
Figure A.1 The results of validation using different thresholds to define the edges. The networks for the differences between automatic and controlled handwriting using unthresholded the functional connectivity (A) and the threshold of p < 0.05 FDR corrected (B).